REMARKS

Claims 1, 2, 10, 12-15, 21, 25, 27, 28, 31, 40-42, 45-48, 56, 57, 77-86, and 101 are pending in the application. Claims 88, 96, 98, and 99 are withdrawn. Claims 3-9, 11, 16-20, 22-24, 26, 29, 30, 32-39, 43, 44, 49-55, 58-76, 87, 89-95, 97, and 100 are cancelled without prejudice or disclaimer. Claim 28 is amended. Accordingly upon entry of the amendment, claims 1, 2, 10, 12-15, 21, 25, 27, 28, 31, 40-42, 45-48, 56, 57, 77-86, and 101 will remain pending in the application.

The claims have been amended to claim more fully the recited subject matter and to make minor editorial changes. Support for the amendments can be found throughout the claims and specification as filed, and is discussed in more detail below. No new matter has been added.

Amendment and cancellation of the claims herein are not to be construed as acquiescence to any rejections/objections set forth in the pending Office Action and/or any previous Office Actions and were done solely to expedite prosecution of the application. Applicants reserve the right to pursue the claims as originally filed or similar claims in this or one or more subsequent patent applications.

Claim Objections

The Office Action at page 5 has objected to claim 28 for reciting the acronym "DEAE." Applicants have amended claim 28 to recite diethylaminoethyl (DEAE).

The Office Action at page 5 has objected to claim 101 for allegedly depending from cancelled claims 54, 63, and 70 and withdrawn claim 47. Applicants respectfully submit that in the Preliminary Amendment filed May 4, 2006, claim 101 was amended to depend from claims 40 and 77.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the claim objections.

Claim Rejections – 35 U.S.C. §103

The Office has rejected claims 1, 2, 10, 12-15, 21, 25, 27, 28, 31, 40-42, 45-48, 56, 57, 77-86, and 101 under 35 USC §103 as being allegedly unpatentable over Hoffer et al. (Journal of Chromatography B, 669:187-196, 1995; "Hoffer") in view of Lim

et al. (The Journal of Infectious Diseases, 188:919-926, 2003; "Lim") and Yang et al. (Crit. Care Med., 30(3):617-622, 2002; "Yang"). Applicants respectfully traverse the rejection.

In order to make out a *prima facie* showing of obviousness, the Examiner must establish that there is some motivation in one or the other of the cited references or in the state of the art at the time the invention was made to combine the references, the combination of references must teach or suggest each and every element of the claimed invention, and there must be some reasonable expectation of success in making and using the invention.

The claims presented herein provide a blood plasma-derived IαIp composition, containing a mixture of inter-alpha inhibitor protein (IαI) and pre-alpha protein (PαI) in a physiological proportion (e.g., a blood plasma-derived IαIp composition about 85% to about 100% pure; having a half-life greater than 1 hour), and a process for producing the IαIp composition.

The Office Action at page 7 alleges that Hoffer teaches the isolation and purification of a human blood plasma product, and that the purification of Hoffer results in "the same product using substantially the same method." (Office action, page 8) Applicants respectfully disagree.

Hoffer teaches the isolation of a Factor IX concentrate. Importantly, Hoffer provides no teaching or suggestion of purifying a blood plasma-derived IαIp composition. One of ordinary skill in the art would not have looked to Hoffer to purify a blood plasma-derived IαIp composition at the time the claimed invention was made. It is only with the benefit of hindsight that the Examiner seeks to combine the disclosure of Hoffer with the teachings of the other cited references. It is well accepted that the use of hindsight is impermissible, and that the current point must be assessed by adopting the position of the artisan as at the priority date of the application in the absence of knowledge of the invention (MPEP §2145). Nevertheless, there is no teaching, suggestion, or motivation to combine the references in the manner suggested by the Examiner to arrive at the invention being claimed.

Even assuming *arguendo* that one would seek to use the teachings of Hoffer to obtain an IαIp composition, the steps recited in Hoffer *per se* are insufficient to obtain

an IαIp composition of the purity claimed. Although the steps used in Hoffer include some of the same steps used by Applicants to obtain the blood plasma-derived IαIp composition of the invention, the purification protocol is different and would not have resulted in the IαIp composition with the purity range recited in the claims. For example, a procedure for producing the blood plasma-derived IαIp composition of the invention from fresh frozen plasma includes the steps of Cryoprecipitation, Solid-phase extraction, Ion exchange chromatography, (optionally, a Second ion-exchange chromatography or Affinity chromatography), and Hydroxylapatite chromatography (Figures 8a and 8b of the specification).

Regarding Hoffer, it would be apparent to one of ordinary skill in the art that one could not purify Factor IX and concurrently purify IαIp. IαIp and Factor IX do not co-fractionate, because IαIp is present in the discarded side-fractions generated during the purification of factor IX (FIX) (see, e.g., the specification at page 9, lines 8-9). Because the protocol of Hoffer follows fractions containing Factor IX, Hoffer would not have been able to purify the IαIp composition described by the applicants using Hoffer's purification protocol. This is especially true given that IαIp can be separated from Factor IX when fractionated by Heparin-Sepharose (Example 4: Purification of IαIp *from a Factor IX Flow Through Fraction*), DEAE-Sepharose (Example 7: Side Fraction *from FIX Purification*; in particular, page 36, lines 7-15), Q Sephadex (Example 7: Side Fraction *from FIX Purification*; in particular, page 37, lines 13-17), DEAE CIM monolith (Example 7: Side Fraction *from FIX Purification*; in particular, page 37, lines 22-24). Thus, Hoffer does not teach or suggest a process for obtaining the IαIp composition being claimed.

As acknowledged on page 7 of the Office Action, Hoffer does not teach "a purified plasma fraction of inter-alpha inhibitory protein composition..." The Examiner has further cited Lim as an alleged remedy for this deficiency of Hoffer. However, Lim does not teach either the IαIp composition being claimed or the method to obtain it.

Specifically, the Office Action at page 8 alleges that "Lim et al teaches the isolation and purification of human plasma-derived inter-alpha inhibitory protein was estimated to greater than 70%." Applicants respectfully disagree. Instead, Lim at page 920, column 2, lines 2-6, plainly states: "The purity of IαIp was estimated to be **~70%** ...

The major contaminants in the IαIp preparation were FVIII and von Willebrand factor." (emphasis added). Lim does not describe their IαIp composition as being greater than 70% pure, as alleged. In Lim, the use of size-exclusion high-performance liquid chromatography produces an IαIp composition that contains FVIII and von Willebrand factor as major contaminants and is, at best, ~70% pure.

The procedures disclosed in Lim could not provide an IαIp composition with the purity range or stability recited in the claims. In contrast, the purification scheme disclosed in the specification (see, e.g., Figures 8a and 8b), is able to to obtain an IαIp composition 85-100% pure using several chromatographic steps (not including size-exclusion chromatography). Lim does not provide the stability (half-life) of the ~70% pure IαIp composition.

The Office Action has further cited Yang to remedy the deficiencies of Hoffer and Lim, but Yang only describes a "procedure involving ion-exchange and size exclusion chromatography" (Office action, at page 8). At best, Yang only additionally teaches an ion exchange step. Yang also does not describe either the purity or the stability (half-life) of the IαIp composition purified by ion-exchange and size exclusion chromatography. The specification is clear that ion-exchange and size exclusion chromatography alone are insufficient to obtain the IαIp compositions being claimed (e.g., 85-100% pure):

> Human IαIp (both IαI and PαI) was isolated as a by-product of a procedure designed for purifying coagulation factor VIII from human plasma. The procedure involves ion exchange and size-exclusion chromatography of cryoprecipitates. **A purity of approximately 70% was achieved after the chromatographic separation.** (Example 2; page 28, lines 1-5; emphasis added)

At best, ion-exchange and size exclusion chromatography alone yields an IαIp that is approximately 70% pure. Thus, Yang does not teach either the IαIp composition being claimed, or the method to obtain it, and does not remedy the deficiencies of Hoffer and Lim.

In sum, there is nothing in any of the cited references or in the state of the art at the time the invention was made that provides one of ordinary skill in the art with motivation to combine Hoffer with Lim and Yang in the manner proffered by the Office.

Hoffer teaches the purification of Factor IX, and, as such, would not result in the purification of the IαIp composition being claimed. Lim and Yang teach the purification of IαIp compositions. One would not be motivated to combine Hoffer with Lim and Yang which teach the purification of two different products.

Nevertheless, assuming *arguendo* that there were some motivation to combine the cited references, the combination of Hoffer, Lim, and Yang does not teach or suggest the claimed invention or how to obtain the claimed invention. Specifically, none of the references describes an IαIp composition either about 85% to about 100% pure (Claim 40 and claims depending therefrom) or having a half-life greater than 1 hour (Claim 47 and claims depending therefrom), and how to obtain a composition with these features (Claim 1 and claims depending therefrom). Regarding IαIp purification, Lim and Yang do not teach the purification steps or the order of the purification steps that allow one to obtain an IαIp composition of the purity claimed.

Even combining all the purification steps taught by the cited references, one skilled in the art would not be able to arrive at a protocol to obtain the IαIp compositions of the invention (see, e.g., Figures 8a and 8b). At best, a protocol based on the teachings of Hoffer, Lim, and Yang would still lack a hydroxylapatite purification step (e.g., in Claim 21), which is important for ensuring the removal of residual contaminating coagulation factors (see, e.g., Example 3; page 33, lines 12-16), and for achieving the purity (85% -100%) and stability (half-life greater than 1 hour) of the IαIp compositions being claimed.

Therefore, because the cited combination of references does not put one of ordinary skill in the art in possession of the claimed invention, one of ordinary skill in the art would not have a reasonable expectation of success in making and using the claimed invention.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1, 2, 10, 12-15, 21, 25, 27, 28, 31, 40-42, 45-48, 56, 57, 77-86, and 101 under 35 U.S.C. §103(a).

CONCLUSION

Applicants respectfully request reconsideration and withdrawal of all rejections and allowance of the application with claims 1, 2, 10, 12-15, 21, 25, 27, 28, 31, 40-42, 45-48, 56, 57, 77-86, and 101 presented herein. If the Examiner believes that a telephone conversation with Applicant's attorney/agent would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney of record.

Applicants submit this paper in response to the Office Action dated November 25, 2009, in the above-referenced patent application. The Director is hereby authorized to charge or credit any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 04-1105, under Order No. 61959(51580).

In view of the above amendment, applicant believes the pending application is in condition for allowance.

Dated: February 25, 2010

Respectfully submitted,

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